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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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HM12/0306

EXAMINER	
SAIDHA, T	
ART UNIT	**PAPER NUMBER**
1652	9

DATE MAILED: 03/06/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)	
09/586744	Harrington et al	
Examiner: T. Saidha	Group Art Unit: 1652	9

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Peri d f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE — 3 — MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 6/2/00 (re-issue).

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disp sition of Claims

☒ Claim(s) 1-73 is/are pending in the application.

Of the above claim(s)____ is/are withdrawn from consideration.

☒ Claim(s) 2-3 is/are allowed.

☒ Claim(s) 1, 4-5, & 7-73 is/are rejected.

☒ Claim(s) 6 is/are objected to.

☐ Claim(s)____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number)____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received:____.

Attachment(s)

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s).____

☐ Interview Summary, PTO-413

☐ Notice of Reference(s) Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Other____

Office Action Summary

DETAILED ACTION

1. Applicants reissue application no. 09/586744, filed 6.2.00 is acknowledged. The original Patent No. 5,874,283, entitled 'Mammalian Flap-Specific Endonuclease', filed May 30, 1995, issued on February 23, 1999.

2. Claims 1-6 of the reissue application are the same as previously (original) patented claims 1-6. New claims 7-73 have been added.

3. Claims 1-73 are under consideration in this examination.

4. A Third Party Protest under C.F.R. 1.291 for this reissue application has been filed (1.3.01, Paper No. 6) has been considered and is made of record.

5. A response to the above cited protest filed 2.15.01 (Paper No. 8) has also been considered and is also made of record.

6. ***Surrendering the Original Patent***

This reissue application was filed without the required offer to surrender the original patent or, if the original is lost or inaccessible, an affidavit or declaration to that effect. The original patent, or an affidavit or declaration as to loss or inaccessibility of the original patent, must be received before this reissue application can be allowed. See 37 CFR 1.178.

7. ***Drawings***

The drawings submitted with this application do not meet the requirements of 37 CFR 1.84. This reissue is considered a new case. Therefore a new set of drawings, starting from FIG. 1.. to FIG. 18.., is required. Delete the word 'NEW' from 'NEW FIG. 1. to NEW FIG. 18' caption.

8. ***Sequence Rules***

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicant Must Provide: An initial or substitute computer readable form (CRF) copy of the "Sequence Listing". An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification. A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

9. ***New Matter***

Claims 7-73 are rejected under 35 U.S.C. 251 as being based upon new matter added to the patent for which reissue is sought. The added material which is not supported by the prior patent is as follows:

(a) Figures 8-18.

(b) Legend to Figures 8-18.

(c) SEQ ID Nos : 64-73

and (e) Inserting text into the specification, describing Example 4, purification of FEN-1, DNA oligonucleotide sequences, Flap endonuclease assay, mobility shift assay for FEN-1 including binding reaction conditions, which was not previously described in the issued patent.

Applicant is required to cancel the new matter in the reply to this Office action.

An application as filed must be complete in it self in order to comply with 35 U.S.C. 112. Material nevertheless may be incorporated by reference, Ex parte Schwarze , 151 USPQ 426 (Bd. App. 1966). An application for a patent when filed may incorporate "essential material" by reference to (1) a U.S. patent or (2) ** >a pending< U.S. application **, subject to the conditions set forth below. "Essential material" is defined as that which is necessary to (1) describe the claimed invention, (2) provide an enabling disclosure of the claimed invention, or (3) describe the best mode (35 U.S.C. 112). In any application which is to issue as a U.S. patent, essential material may not be incorporated by reference to (1) patents or applications published by foreign countries or a regional patent office, (2) non - patent publications, (3) a U.S. patent or application which itself incorporates "essential material" by reference, or (4) a foreign application. See In re Fouche , 439 F.2d 1237, 169 USPQ 429 (CCPA 1971).

Nonessential subject matter may be incorporated by reference to (1) patents or applications published by the United States or foreign countries or regional patent offices, (2) prior filed, commonly owned U.S. applications, or (3) non - patent publications. Nonessential subject matter is subject matter referred to for purposes of indicating the background of the invention or illustrating the state of the art.

Mere reference to another application, patent, or publication is not an incorporation of anything therein into the application containing such reference for the purpose of the disclosure

required by 35 U.S.C. 112, first paragraph. In re de Seversky , 474 F.2d 671, 177 USPQ 144, (CCPA 1973).

Claims 7-73 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 7-73 are directed to method steps using 'double-flap' structures, hybridization complexes and kits, which claims have no support in the specification of the issued patent. The method steps claimed had no basis or clearly outlined in the prior application or the issued patent. Claims also lack Flap endonuclease assay for measuring cleavage activity as well as hybridization conditions for use in complexes and kits.

10. Claims 7-73 are rejected under 35 U.S.C. 251 as not being for the same general invention patented in the original patent. The invention patented in the original patent is to an isolated polynucleotide encoding a polypeptide identified by SEQ ID NOS : 1 and 3. Claims to method of cleaving a polynucleotide, detecting a nucleic acid in a sample, a hybridization complex of first and second bridge polynucleotides, and a kit for detecting nucleic acids were not present in the original patent or its prosecution. As noted in Applicants declaration, "At the time the original patent issued, Applicants failed to recognize that the application as filed disclosed patentable invention beyond those originally and ultimately claimed. The originally disclosed but unclaimed inventions are embodied in claims 7-73..". By Applicants own admission the invention of claims 7-73 are additional inventions which were not claimed in a continuing application (CON, CIP or DIV) prior to issuance of Patent

No. 5,874,283. Applicants' extensive amendments to the specification to provide proper support for the newly claimed inventions is evidence that they were not adequately disclosed in a manner as to provide one skilled in the art a recognition of the newly claimed invention. See MPEP 1412.01.

11. ***specification***

Claim 14, line 1, recites 'is comprises'. Delete 'is'.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Written Description

12. Claims 7-10, 14-27, 31-44, 48-70 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The instant claims are directed to a method of cleaving a polynucleotide (claims 7-10, 14-27), a method of detecting the presence of target nucleic acid (claims 31-44), a hybridization complex (claims 48-58) and a kit for detecting the presence of a target nucleic acid (claims 59-70). The instant claims contain no limitations that define the structure of the claimed endonuclease (or FEN-1 SEQ ID NO :), used for cleaving a polynucleotide comprising the 3' and 5' regions or that used in the detection method or for hybridization complex and kit. The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a

description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original).

Just as the claims at issue in UC v. Lilly defined the invention by the function of the claimed DNA (encoding insulin), the instant claims define the endonuclease/DNA only by their functional properties. The court held this sort of functional definition insufficient. "In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly such a formula is normally an adequate description of the claimed genus. In claims to genetic material, however, a generic statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA,' without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is." UC v. Lilly, at *24-*25.

The instant claims are not supported by an adequate written description for the same reasons that the claims in UC v. Lilly were found to be inadequately supported.

13. ***Utility***

Claims 51-58 are rejected under 35 U.S.C. § 101 because the claimed invention is not supported by specific and substantial asserted utility or a well established utility. The claims recite a hybridization complex comprising a first and second polynucleotide. The specification does not provide support to make or use the claimed hybridization complexes.

Claims 51-58 are also rejected under 35 U.S.C. § 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial utility or a well established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention so that it would operate as intended without undue experimentation.

14. Claims 7-73 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

With regard to claims 7-73, directed to a nucleic acid probe that specifically hybridizes to another or target nucleic acid(s), Applicants have not sufficiently defined the conditions under which the hybridizations are to take place. Nucleic acid hybridization assays are extremely sensitive to the conditions in which they are performed. The buffer composition, pH, temperature, length of time, salt concentrations, quality and source of template nucleic acid, are all variables which determine the reproducibility of a given hybridization experiment. Given the unpredictability of the art and the

nature of hybridization experiments in general, it is not sufficient to merely cite hybridization without a clear and explicit recitation of the conditions associated with the hybridization. For example, the definition of stringency as it pertains to hybridization conditions is subject to interpretation and is different from laboratory to laboratory. Therefore, without a clear and explicit recitation of the conditions which were actually used by Applicants in isolating the claimed polynucleotides which hybridize to the disclosed sequences, the skilled artisan would not be able to practice the claimed invention and would not be reasonably apprised of the metes and bounds of the claimed invention. Without such guidance, the experimentation left to those skilled in the art is undue.

15. Claim 7 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: cleaving the 5' flap labeled structure by FEN-1, releasing the nucleotide in the flap strand; incubating with FEN-1 and detection the release of nucleotides (polynucleotide) of the flap strand and quantifying the released label as a measure of abundance of the target polynucleotide in the sample. The clarity of the steps is important.

16. ***Rejection under 35 U.S.C. 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4-5 are rejected under 35 U.S.C. 102(a) as being anticipated by Murray et al. [Mol. Cel. Biol. 14(7) : 4878-4888, July 1994, IDS). Murray et al. using degenerate PCR teach the cloning of human homolog of the *rad2* gene. The *rad2* gene was identified as a 380-amino acid coding sequence. The nucleotide sequence is shown in Figure 3(B). This gene (human homolog of the *rad2*) encode an endonuclease which is 99.7% identical to human FEN-1 (Applicants' SEQ ID NO : 1) and a fragment which without a size limitation will inherently be endonucleotically active or have endonuclease activity. Expression vector, host cell are also described. The claims are anticipated by the reference for the fragment language.

17. Claims 7-9 & 51 are rejected under 35 U.S.C. 102(b) as being anticipated by Lyamichev et al. [Science 260 : 778-783, May 7, 1993, IDS]. Lyamichev et al. teach a structure specific endonucleolytic cleavage of nucleic acids by DNA polymerases. (See figure 1A.). Incubation of the structure shown in Fig. 1A with 5' nuclease of DNAP. Taq. resulted in the cleavage of the nucleic acid from the 5' region (claims 7-9), and would hybridize to probes comprising 3' & 5' regions (claim 51). The claims are written so broadly as to be anticipated by the reference.

18. ***Rejection under 35 U.S.C. 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the

subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 7-73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harrington and Lieber [EMBO JOURNAL, (**1994 Mar 1**) 13 (5) 1235-46, IDS]. Harrington et al. teach a DNA flap as a bifurcated structure composed of double-stranded DNA and a displaced single-strand. To identify DNA flap cleaving activities in mammalian nuclear extracts, the reference teaches an assay utilizing a synthetic DNA flap substrate. This assay has allowed the first purification of a mammalian DNA structure-specific nuclease. The enzyme described here, flap endonuclease-1 (FEN- 1), cleaves DNA flap strands that terminate with a 5' single-stranded end. As expected for an enzyme which functions in double-strand break repair flap resolution, FEN-1 cleavage is flap strand-specific and independent of flap strand length. Furthermore, efficient flap cleavage requires the presence of the entire flap structure. Substrates missing one strand are not cleaved by FEN-1. In addition to endonuclease activity, FEN-1 has a 5'-3' exonuclease activity which is specific for double-stranded DNA. The endo- and exonuclease activities of FEN-1 are discussed in the context of DNA replication, recombination and repair. (see abstract, Figure 1, DNA substrate oligonucleotides, cleavage of flap structure derivatives, Figures 5-10 and discussion).

The teachings of the reference identifies a purified nuclease from mouse which is specific for DNA flap structures. The cleavage of the 5'-flaps by FEN-1 (flap endonuclease 1) was unrelated in sequence (see discussion, page 1243, column 1-2), was independent of flap strand length (varying nucleotide length, may be 1, 1-10 or 20) and always occurred in a strand specific fashion such that

only 5' flap strand of the polynucleotide was cleaved, and monitored by detecting label contained in the 5'-end (see Fig. 5 and 7, for example.).

The reference does specifically teach the method steps as claimed, however uses an obvious variation of cleaving a polynucleotide using a FEN-1 and measuring the detectable radio-label, which are visualized by autoradiography.

It would have been obvious for one of ordinary skill in the art, to recite or make the obvious method steps variations or changes using the detailed methodology presented in the cited reference of Harrington et al. by cleaving the polynucleotide using the FEN-1 polypeptide or catalytically active fragments thereof or substitute the FEN-1 polypeptide with other known endonucleases (or that of specific SEQ ID nos.) and monitor the radiolabeled product for the detection of target nucleic acid in a sample (claims 7-50), using the hybridization complexes (claims 51-58) as FEN-1 substrates (many of which are taught by the Harrington et al.) or develop a kit (claims 59-73) using the method outlined above for the detection of target nucleic acid. One of ordinary skill in the art would have been motivated to make or modify the method suitably, in view of the suggested importance of the roles of FEN-1 in DNA replication, DNA repair and recombination (see introduction), and do so with a reasonable expectation of success.

19. Claim 6 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

20. Claims 2-3 are allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tekchand Saidha (Ph.D.) whose telephone number is (703) 305-6595. The examiner can normally be reached on Monday-Friday from 8:15am to 4:45pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy, can be reached at (703) 308-3804. The fax phone number for this Group in the Technology Center is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Tekchand Saidha
Patent Examiner, Art Unit 1652
March 1, 2001

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